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ORIGINAL ARTICLE

Evaluation of pulmonary function in renal transplant recipients and chronic renal failure patients undergoing maintenance hemodialysis

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Abstract *Background:* Impaired pulmonary function in patients on hemodialysis may be caused by an underlying pulmonary disease, however the effects of hemodialysis treatment and kidney transplantation are not well understood.

Aim of the work: The aim of this study was to evaluate pulmonary function among patients with chronic renal failure (CRF) undergoing hemodialysis and patients with kidney transplant.

Patients and methods: This study was conducted on 60 subjects. They were classified into 3 groups: Hemodialysis group (HDG) included 20 patients with end stage renal disease (ESRD) on regular hemodialysis for at least six months and were clinically stable. Transplant group (TG) included 20 patients who had undergone kidney transplant at least six months earlier and were also clinically stable. Control group (CG) included 20 apparently healthy subjects. All subjects underwent pulmonary function testing; including resting spirometry included flow volume loop and Maximal Voluntary Ventilation (MVV), measurement of lung volumes and diffusing capacity for carbon monoxide (DLCO) using single breath technique, Six Minute Walking Test (6MWT) and arterial blood gases (ABG).

Results: There was a significant difference between HDG, TG and CG regarding FVC% of predicted, FEV1% of predicted, FEF 25–75% of predicted, PEF% of predicted and MVV% of predicted. Also there was a statistically significant difference between HDG, TG and CG regarding RV% of predicted, TLC% of predicted and RV/TLC%. Although FVC% of predicted and FEV1% of predicted were within the normal range in the 3 studied groups, there was a statistically

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significant reduction in these spirometric parameters in HDG more than that in the TG and CG, also reduction in TG more than CG. FEF 25–75% of predicted was less than normal in HDG and was within the normal range in TG and CG, also RV% of predicted and TLC% of predicted were increased in HDG more than that in TG and CG. Regarding DLco% of predicted we found significant differences between the 3 studied groups. It was lower in HDG than in TG and CG. Also the same results we found regarding Dlco/VA% of predicted. There were statistically significant differences among the studied groups regarding 6MWT. Regarding ABG although all values were within normal levels, Pao₂ in HDG was less than that in TG and CG.

Conclusion: There is impairment of lung function in patients with CRF undergoing hemodialysis. The main changes are small airway obstruction, reduction in carbon monoxide transfer and diminished 6MWT that were not completely improved in the kidney transplant patients.

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Introduction

Chronic renal diseases are associated with a variety of respiratory manifestations. Pulmonary edema, pleural disease, pulmonary calcification, and sleep apnea syndrome have been documented in patients with chronic renal failure. Furthermore, treatment with hemodialysis also produces transient changes in pulmonary gas exchange [1]. Impaired pulmonary function in patients on hemodialysis may be caused by an underlying pulmonary disease, however, the impact of uremia and the effects of hemodialysis treatment are not well understood. Several mechanisms may impair pulmonary function and alter bronchial responsiveness in patients on long term regular hemodialysis treatment, some of which are trapping of neutrophils, increased extra-vascular lung water, left ventricular hypertrophy, metastatic lung calcification, and iron deposition [2,3]. On the other hand, hemodialysis can result in better respiratory function [4]. The muscles responsible for respiratory function, such as the diaphragm and intercostals, among others, are classified as skeletal muscles and may show decreases in muscle strength and endurance properties resulting from uremic myopathy. Some authors [5] who have studied the involvement of uremia in the diaphragm have concluded that loss of strength occurs through severe uremia. The ventilatory deficit due to this impairment in respiratory muscles, combined with other lung tissue impairments, compromises the functioning of this system, thereby contributing toward decreased lung capacity [6,7]. During hemodialysis, the majority of patients develop a reduction in arterial PO₂. The arterial PO₂ falls within a few minutes of initiation of dialysis by 10–15 mmHg, reaches a nadir after 30–60 min, and persists for the duration of the procedure [8–10]. The severity of hypoxemia varies according to the type of dialysis membrane and the chemical nature of the dialysate buffer [11,12]. Several mechanisms have been proposed to explain the decrease in arterial PO₂: (1) a shift in the oxyhemoglobin dissociation curve caused by the increase in pH during the procedure, (2) depression of central respiratory output due to alkalosis, (3) oxygen diffusion impairment, (4) ventilation–perfusion mismatching due to stasis of leukocytes in small pulmonary vessels, and (5) hypoventilation due to carbon dioxide excretion via the dialysate. Some changes found in patients with CKF undergoing dialysis are also observed in transplant patients, even after restoration of kidney function. These changes can be partially attributed to immunosuppressive therapy, which

commonly uses corticosteroids. This medication is associated with decreased synthesis and increased protein catabolism, which could hamper full return of the functions of kidney transplant patients [13].

The aim of the work

The aim of this study was to evaluate pulmonary function (including resting spirometry included flow volume loop and Maximal Voluntary Ventilation (MVV), measurement of lung volumes and diffusing capacity for carbon monoxide), 6MWT and ABG among patients with CRF undergoing hemodialysis and patients with kidney transplant.

Materials and methods

This study was conducted in King Fahd hospital in Almadinah Al Monawarah, Kingdom Saudi Arabia from December 2011 to December 2012 on a cohort of 60 subjects. The study protocol was approved by the local ethics committee. Informed consent was obtained from the patients. The subjects were classified into 3 groups:

Group I: hemodialysis group (HDG): included 20 patients with end stage renal disease (ESRD) on regular hemodialysis. They included (7 men and 13 women). These individuals had been undergoing hemodialysis regularly for at least six months. They were clinically stable, without anemia, and were under clinical follow-up. Group II: transplant group (TG): Included 20 patients (8 men and 12 women) who had undergone kidney transplant at least six months earlier. These patients were stable from a clinical and surgical point of view and were also under regular clinical follow-up. Group III: control group (CG): included 20 apparently healthy subjects (9 men and 11 women). These were of the same age and gender as the other two groups and fulfilled the same criteria for non-inclusion.

The exclusion criteria were history of respiratory diseases, and cardiac insufficiency, being a smoker or ex-smoker, current respiratory infections, musculoskeletal disorders, and those who were unable to cooperate.

All subjects were subjected to:

1. Thorough history taking and full clinical examination.
2. Chest X-ray picture was taken before each study, and if it was abnormal, the patient was eliminated from the study.

3. For hemodialysis group (HDG): all patients had undergone hemodialysis for at least six months before the first tests were done. Pulmonary function, 6MWT and ABG studies were carried out on the day after hemodialysis. The time interval between the end of hemodialysis and the post-dialysis study was 8–16 h. Blood transfusions were not given.
4. For transplant group (TG): the same studies were done at least six months after renal transplantation at a time when the function of the transplanted kidney was good as defined by a blood urea nitrogen level less than 40 mg percent or creatinine clearances over 30 ml/min.
5. Also all subjects underwent pulmonary function testing; including resting spirometry included flow volume loop and Maximal Voluntary Ventilation (MVV) [14], measurement of lung volumes [15] and diffusing capacity for carbon monoxide (DLCO) using the single breath technique [16] which were performed using computerized equipment (V. Max 225 Auto box) sensor medics system. Ambient temperature and pressure were entered with the patient data (age in years, weight in kilograms, height in centimeters and sex). So that all results were calculated as percent of predicted except for FEV1/FVC%.
6. Six-Minute Walk Test [17]: the test was conducted between 10 a.m. and 4 p.m. for all subjects. A thirty-meter flat, obstacle-free corridor with a chair placed at either end was used. Patients were instructed to walk as far as possible to cover the longest possible distance over six minutes under supervision. The patient was instructed that the object of this test is to walk as far as possible for 6 min through walking back and forth in this hallway. You are permitted to slow down, to stop and to rest as necessary. You may lean against the wall while resting, but resume walking as soon as you can.
7. Arterial blood was analyzed for pH, PaO₂ and PaCO₂ with an Instrumentation Laboratory blood gas analyzer, RAPID Lab 248/348 Systems.
8. Patients were on regular hemodialysis 3 times/week, using Fresenius 4008s, each session 4 h. Dry weight adjusted according to clinical assessment each visit. Renal transplantation was carried out according to standard procedures. Transplanted patients had stable graft function with no history of rejection in the last 3 months, or admission for hospital. All of them were on cyclosporine, mycophenil mofetil and prednisolone.

Statistical analysis

Statistical analysis was performed using MedCalc Software Version 12.2.1 (MedCalc Software bvba. MedCalc Software, Broekstraat 52, 9030 Mariakerke, Belgium). The results were shown as means (and standard deviations). To compare the groups in relation to parameters with normal distribution, one-way ANOVA with post-hoc Fisher's LSD (least significant difference) was used. To compare two independent samples we used an unpaired *t*-test. A *p*-value of <0.05 was considered significant.

Results

See Tables 1–3.

Discussion

The relationships between the lungs and the kidneys are clinically important ones in both health and disease. Chronic renal failure may affect respiratory function [18]. Pulmonary dysfunction may be the direct consequence of circulating uremic toxins or may result indirectly from volume overload, anemia, immune suppression, extra osseous calcification, malnutrition, electrolyte disorders, and/or acid–base imbalances [4]. In our study we found that there was a significant difference between HDG, TG and CG regarding FVC% of predicted ($p < 0.001$, mean \pm SD of HDG was 80.65 ± 3.51 , TG was 82.55 ± 3.57 and for CG was 84.80 ± 2.14), FEV1% of predicted ($p = 0.001$, mean \pm SD of HDG was 80.45 ± 3.56 , TG was 82.45 ± 2.74 and for CG was 84.25 ± 2.84), FEF 25–75% of predicted ($p < 0.001$, mean \pm SD of HDG was 74.40 ± 2.96 , TG was 82.25 ± 4.41 and for CG was 84.30 ± 1.89), PEF% of predicted ($p < 0.001$, mean \pm SD of HDG was 80.45 ± 4.12 , TG was 84.05 ± 3.21 and for CG was 87.75 ± 2.22) and MVV% of predicted ($p < 0.001$, mean \pm SD of HDG was 76.75 ± 4.08 , TG was 81.15 ± 2.91 and for CG was 87.30 ± 2.41). Also there was a statistically significant difference between HDG, TG and CG regarding RV% of predicted ($p < 0.001$, mean \pm SD of HDG was 118.50 ± 9.06 , TG was 116.05 ± 8.42 and for CG

Table 1 Characteristics of the studied subjects.

	Hemodialysis (HDG) ($n = 20$)	Transplantation (TG) ($n = 20$)	Control (CG) ($n = 20$)	<i>p</i> -Value	<i>F</i> Value
Age (years)	42.40 ± 3.89	38.60 ± 4.51	39.450 ± 6.48	$p = 0.054$	3.079
Sex (M/F)	7/13	8/12	9/11		
Smoking history	Non	Non	Non		
HB (gm/dl)	10.20 ± 0.77	11.95 ± 0.83	13.20 ± 1.24	$p < 0.001$	48.524
Albumin (g/L)	27.70 ± 3.40	29.85 ± 1.73	34.45 ± 2.52	$p < 0.001$	34.085
Urea (mmol/L)	12.05 ± 3.02	9.25 ± 2.27	10.25 ± 2.19	$p = 0.003$	6.332
Creatinine (μ mol/L)	317.75 ± 84.77	118.55 ± 27.23	88.55 ± 9.90	$p < 0.001$	116.013
Calcium (mmol/L)	2.185 ± 0.15	2.035 ± 0.18	1.721 ± 2.24	$p = 0.518$	0.665
Phosphorous (mmol/L)	0.945 ± 0.13	1.055 ± 0.23	0.80 ± 0.22	$p < 0.001$	8.81

ANOVA $p < 0.01$ between groups; post-hoc Fisher's LSD (least significant difference).

Age (years) ($F = 3.079$, $p = 0.054$). HB gm/dl ($F = 48.524$, $p < 0.001$; LSD CG > HDG; CG > TG; TG > HDG). Albumin ($F = 34.085$, $p < 0.001$; LSD CG > HDG; CG > TG; TG > HDG). Urea ($F = 6.332$, $p = 0.003$; LSD CG < HDG; TG < HDG). Creatinine ($F = 116.013$, $p < 0.001$; LSD CG < HDG; TG < HDG). Calcium ($F = 0.665$, $p = 0.518$). Phosphorous ($F = 8.81$, $p < 0.001$; LSD CG < HDG; CG < TG).

Table 2 Comparison between different studied groups as regards pulmonary function and 6MWT.

	Hemodialysis (HDG) (<i>n</i> = 20)	Transplantation (TG) (<i>n</i> = 20)	Control (CG) (<i>n</i> = 20)	<i>p</i> -Value	<i>F</i> Value
FVC(%pred)	80.65 ± 3.5135	82.55 ± 3.5759	84.80 ± 2.142	<i>p</i> < 0.001	8.713
FEV1 (%pred)	80.45 ± 3.5600	82.45 ± 2.7429	84.25 ± 2.8447	<i>p</i> = 0.001	7.701
FEV1/FVC	81.35 ± 1.8144	82.60 ± 2.0622	82.10 ± 2.1981	<i>p</i> = 0.156	1.919
FEF 25–75 (%pred)	74.40 ± 2.9629	82.25 ± 4.4114	84.30 ± 1.8946	<i>p</i> < 0.001	51.474
PEFR (%pred)	80.45 ± 4.1228	84.05 ± 3.2196	87.75 ± 2.2213	<i>p</i> < 0.001	24.751
MVV (%pred)	76.75 ± 4.0766	81.15 ± 2.9069	87.30 ± 2.4083	<i>p</i> < 0.001	54.582
RV (%pred)	118.50 ± 9.06	116.05 ± 8.42	107.00 ± 4.94	<i>p</i> < 0.001	12.40
TLC (%pred)	88.70 ± 6.41	86.10 ± 4.70	83.75 ± 4.55	<i>p</i> = 0.017	4.38
RV/TLC (%pred)	133.72 ± 6.62	134.87 ± 8.05	127.93 ± 5.54	<i>p</i> = 0.004	5.96
DLco (%pred)	75.15 ± 14.3317	83.55 ± 4.1861	86.20 ± 1.8806	<i>p</i> < 0.001	8.818
DLco/AV (%pred)	70.70 ± 17.0390	84.30 ± 3.6288	86.45 ± 1.8489	<i>p</i> < 0.001	14.260
6MWT (meter)	395.20 ± 60.43	459.00 ± 68.17	535.55 ± 63.68	<i>p</i> < 0.001	24.436

ANOVA *p* < 0.01 between groups; post-hoc Fisher's LSD (least significant difference).

FVC (*F* = 8.713, *p* < 0.001; LSD CG > HDG; CG > TG). FEV1 (*F* = 7.701, *p* < 0.001; LSD CG > HDG; TG > HDG). FEV1/FVC% (*F* = 1.919, *p* < 0.156). FEF 25–75 (*F* = 51.474, *p* < 0.001; LSD CG > HDG, TG > HDG). PEFR (*F* = 24.751, *p* < 0.001; LSD CG > HDG; CG > TG; TG > HDG). MVV (*F* = 54.582, *p* < 0.001; LSD CG > HDG; CG > TG; TG > HDG). RV (%pred) (*F* = 12.40, *p* < 0.001; LSD CG < HDG; CG < TG). TLC (%pred) (*F* = 4.38, *p* = 0.017; LSD CG < HDG). RV/TLC% (*F* = 5.96, *p* = 0.004; LSD CG < HDG; CG < TG). DLco (%pred) (*F* = 8.818, *p* < 0.001; LSD CG > HDG; TG > HDG). DLco/AV (%pred) (*F* = 14.260, *p* < 0.001; LSD CG > HDG; TG > HDG). 6MWT (*F* = 24.436, *p* < 0.001; LSD CG > HDG; CG > TG; TG > HDG).

Table 3 Comparison between different studied groups as regards arterial blood gases (ABG):

	Hemodialysis (HDG) (<i>n</i> = 20)	Transplantation (TG) (<i>n</i> = 20)	Control (CG) (<i>n</i> = 20)	<i>p</i> -Value	<i>F</i> Value
PH	7.37 ± 0.020	7.37 ± 0.022	7.38 ± 0.024	<i>p</i> = 0.311	1.191
Pao2 (mmHg)	80.45 ± 3.63	82.05 ± 1.93	85.65 ± 2.62	<i>p</i> < 0.001	17.872
Paco2 (mmHg)	38.55 ± 2.93	40.40 ± 3.65	39.75 ± 1.74	<i>p</i> = 0.12	2.121
Hco3 (mEq/L)	21.00 ± 1.17	19.90 ± 0.79	22.00 ± 1.49	<i>p</i> = 0.35	1.06

ANOVA *p* < 0.01 between groups; post-hoc Fisher's LSD (least significant difference).

PH (*F* = 1.191, *p* = 0.311). Pao2 (*F* = 17.872, *p* < 0.001; LSD CG > HDG; CG > TG; HDG > TG). Paco2 (*F* = 2.121, *p* = 0.12). Hco3 (*F* = 1.06, *p* = 0.35).

was 107.00 ± 4.94), TLC% of predicted (*p* = 0.017, mean ± SD of HDG was 88.70 ± 6.41, TG was 86.10 ± 4.70 and for CG was 83.75 ± 4.55) and RV/TLC% (*p* = 0.004, mean ± SD of HDG was 133.72 ± 6.62, TG was 134.87 ± 8.05 and for CG was 127.93 ± 5.54). Although FVC% of predicted and FEV1% of predicted were within the normal range in the 3 studied groups, there was a statistically significant reduction in these spirometric parameters in HDG more than that in the TG and CG, also reduction in TG more than CG. These results are in agreement with those of Kovacevic et al. [19] who found that patients who are on long term hemodialysis show a significant decline in FVC. We found also FEF 25–75% of predicted was less than normal in HDG and was within the normal range in TG and CG this means that there was a small airway obstruction in HDG, also RV% of predicted and TLC% of predicted were increased in HDG more than that in TG and CG. These spirometry findings suggest that a small 'airway disease cause increased RV and TLC in HDG. These results are in agreement with those of Karacon et al. [20] who found significantly higher residual volume and total lung capacity in the hemodialysis and peritoneal dialysis groups than in the transplantation group. Forced expiratory flow between 25% and 75% of vital capacity was slightly be-

low normal in the dialysis patients. Also Kalender et al. [21] studied the effect of renal transplantation on pulmonary function and found that peak expiratory flow (PEF 25–75) was decreased in the uremic group than that in the transplant group. Another component in the spirometric evaluation was MVV% of predicted, it was less than normal value in HDG and was within normal values in TG and CG (but TG less than CG) this means that HDG and TG have limitation to their ventilatory capacity. These results match with those of Zarday et al. [22] and Guleria et al. [23] who concluded that the improvement in MVV in the post transplant group was statistically significant and found that this increase, however, may reflect a general improvement in the patients' physical condition and muscle strength, rather than any specific pulmonary improvement. Also Bush and Gabriel [24] found that the MVV was lower in the HDG and TG than in the CG, thus concluded that patients with CKF undergoing dialysis and kidney transplant patients have limitations to their ventilatory capacity. Wanic-Kossowska [25] evaluated 18 patients on hemodialysis and found a reduced maximal breathing capacity and an increased residual volume among them.

Regarding diffusion capacity for carbon monoxide (DLco% of predicted) we found significant differences be-

tween the 3 studied groups. It was lower in HDG than in TG and CG ($p < 0.001$, mean \pm SD of HDG was 75.15 ± 14.33 , TG was 83.55 ± 4.18 and for CG was 86.20 ± 1.88). Also we found similar results regarding Diffusion per Unit of Alveolar Volume (DLco/VA% of predicted). HDG was less than TG and CG ($p < 0.001$, mean \pm SD of HDG was 70.70 ± 17.039 , TG was 84.30 ± 3.63 and for CG was 86.45 ± 1.85) this was in accordance with Bush and Gabriel [24] who concluded that abnormalities of lung function are very common in renal failure, the major finding being a reduction in carbon monoxide transfer factor. They believed that the likeliest cause of the low carbon monoxide transfer factor before transplantation is subclinical pulmonary edema or interstitial fibrosis secondary to recurrent pulmonary edema. Pulmonary edema would be favored by increased vascular permeability, fluid overload, and a low serum albumin concentration. Dujic et al. [26] found a reduction of TLCO in 25 patients receiving hemodialysis, which was related to anemia given that TLCO decrease reversed with blood transfusion. Zarday et al. [22] found impairment of the diffusion capacity for carbon monoxide in DG and this showed a slight improvement in post-transplant period and explained this by the anemia accompanying renal disease and not to azotemia itself. Herrero et al. [27] concluded that in patients maintained on hemodialysis for a long time, there is a selective impairment in pulmonary diffusing capacity. Kalender et al. [21] found that there was a slight decrease in the diffusion capacity in the uremic group and normal diffusion capacity in the transplanted group.

In the present study we evaluated 6MWT among the studied groups and we found that there were statistically significant differences among the studied groups ($p < 0.001$, mean \pm SD of HDG was 395.20 ± 60.43 , TG was 459.00 ± 68.17 and for CG was 535.55 ± 63.68). These results are in agreement with those of Oh-Park et al. [28] who evaluated the 6MWT and found that the CKF patients walked distances that were shorter than what is considered to be normal, with a mean of 405 m for dialysis patients (a value slightly lower than what was found in the present study). Cury et al. [29] studied the pulmonary function and the functional capacity among patients with CKF undergoing dialysis and among kidney transplant patients and found that the 6MWT in their study demonstrated that individuals in the HDG and TG had worse results than did those in the CG. Our results were in disagreement with Becker-Cohen et al. [30] who evaluated the 6MWT in children and young adults with CKF and with kidney transplants who were still undergoing dialysis and found values within normality. Although there were no specific predictive values for children, they found that on an average, the distance that they were able to walk was only 100 m less than what the adults who were evaluated could achieve. Those authors therefore considered this result to be normal.

Table 3 showed comparison between the different studied groups as regards arterial blood gases (ABG). Although all values were within normal levels, PaO₂ in HDG was less than that in TG and CG ($p < 0.001$, mean \pm SD of HDG was 80.45 ± 3.63 , TG was 82.05 ± 1.93 and for CG was 85.65 ± 2.62). Morales et al. [31] studied the lung function pre- and post renal transplantation on 21 patients and determined spirometry including lung volumes, arterial blood gases, DLCO and DLco/AV before and 3, 6, and 12 months after transplantation. They concluded that spirometric and blood gases data remained within reference levels during the follow

up. Ahluwalia et al. [32] studied pulmonary functions during peritoneal dialysis and found no significant differences in PaO₂, PaCO₂ or PH during any phase of the study. Herrero et al. [27] studied pulmonary diffusion capacity in chronic dialysis patients and found that PaO₂ and PaCO₂ were similar in all the groups with no significant differences. PH and bicarbonate were within normal values in all groups although it is less in group 1 without dialysis than in group 2 and 3 with hemodialysis.

Conclusions

According to our findings, it can be concluded that patients with CRF undergoing hemodialysis and patients with kidney transplantation show lower values regarding lung function and 6MWT than those of the general population and that patients undergoing hemodialysis have greater impairment of lung function and 6MWT than do kidney transplant patients. Blood gas data remained within normal reference levels although there was a significant difference between the 3 groups regarding PaO₂.

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